Translation

PCT Application
PCT/JP2003/004396

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3039WO 0 P	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP03/04396	International filing date (*day/month/year*) 07 April 2003 (07.04.03)	Priority date (*day/month/year*) 08 April 2002 (08.04.02)
International Patent Classification (IPC) or national classification and IPC A61K31/215, 31/223, 31/245, 31/27, 31/277, 31/41, 31/4192, 31/4196, 31/428, 45/00, A61P1/00, 1/04, 1/06, 1/16, 3/02, 3/06, 3/10, 3/14, 7/02, 7/06, 9/02, 9/04, 9/10, 9/14, 11/06, 13/12, 15/08, 17/00, 02, 16, 19/02, 06, 08, 21/04, 25/00, 08, 18, 20, 28, 27/02, 16, 29/00, 31/04, 10, 12, 16, 18, 22, 33/06, 35/00, 37/02, 43/00, C07D249/06, 08, 257/04, 275/06		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09 May 2003 (09.05.03)	Date of completion of this report 24 September 2003 (24.09.2003)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5, 14, 15, 20

because:

☒ the said international application, or the said claims Nos. 5, 14, 15, 20 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 5, 14, 15, 20.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of III. 1.

Claims 5, 14, 15 and 20 pertain to methods for treatment of the human body by therapy, and thus relate to subject matter which does not require international preliminary examination by this International Preliminary Examining Authority, under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

See supplemental sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

The "special technical feature" of claims 1-4 and 6 relates to prophylactic therapeutic agents for severe sepsis in which the active ingredient is a cycloalkene compound.

The "special technical feature" of claims 7-13 and 16-19, on the other hand, relates to TLR signal inhibitors.

There is thus no technical relationship among these inventions involving one of more of the same or corresponding special technical features; they are, therefore, not so linked as to form a single general inventive concept.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-4, 6-13, 16-19	NO
Inventive step (IS)	Claims		YES
	Claims	1-4, 6-13, 16-19	NO
Industrial applicability (IA)	Claims	1-4, 6-13, 16-19	YES
	Claims		NO

2. Citations and explanations

Document 1: JP 2001-261557 A (Takeda Chemical Industries), 26 September 2001

Document 2: WO 99/46242 A1 (Takeda Chemical Industries), 16 September 1999

Document 3: WO 01/010826 A1 (Takeda Chemical Industries), 15 February 2001

Document 4: WO 99/25834 A1 (Genentech, Inc.), 27 May 1999

Document 5: WO 99/20756 A2 (Genentech, Inc.), 29 April 1999

Claims 1-4, 6-13 and 16-19

The inventions set forth in claims 1-4, 6-13 and 16-19 are not novel and do not involve an inventive step in the light of documents 1-3, cited in the international search report.

Document 1 discloses compounds represented by a formula (I), salts thereof and prodrugs thereof, which act to suppress nitrogen monoxide (NO) production, act to suppress the production of inflammatory cytokines such as TNF-α, IL-1 and IL-6, and are useful as prophylactic and therapeutic agents for disorders such as heart disease,

autoimmune disorders, inflammatory disorders, central nervous disorders, infections, sepsis and septic shock (claims and paragraph [0055]).

Document 2 discloses cycloalkene derivatives represented by a formula (Ia) which act to suppress the production of nitrogen monoxide (NO) by inducible nitric oxide synthase and/or act to suppress the production of inflammatory cytokines such as TNF-α, IL-1 and IL-6, and are useful as prophylactic and therapeutic agents for disorders such as heart disease, autoimmune disorders, inflammatory disorders, central nervous disorders, infections, sepsis and septic shock (claims and page 56, line 19 to page 57, line 26).

Document 3 discloses compounds represented by a formula (I), and salts thereof and prodrugs thereof, which have low toxicity, act to suppress the production of nitrogen monoxide (NO) and act to suppress the production of inflammatory cytokines such as TNF-α, IL-1 and IL-6, and are useful as prophylactic and/or therapeutic agents for disorders of mammals such as heart disease, autoimmune disorders, inflammatory disorders, central nervous disorders, infections, sepsis and septic shock (claims and page 41, line 18 to page 42, line 19).

Although documents 1-3 do not mention "prophylactic therapeutic agents for severe sepsis", page 41 of the description of the present application indicates that the "prophylactic therapeutic agents for severe sepsis" in the inventions set forth in claims 1-4 and 6 function due to their action in suppressing the production of NO and action in suppressing production of inflammatory cytokines. Therefore, compounds, salts and prodrugs disclosed in documents 1-3, which have the same suppressing actions, clearly can also treat/prevent severe sepsis and not only sepsis.

Moreover, although documents 1-3 do not mention TLR signal inhibitors, specific manifestations of TLR signal inhibitors include agents for suppressing production of NO and/or inflammatory mediators such as cytokines (see page 59 of the description of the present application). Therefore, the inventions set forth in claims 7-13 and 16-19 are indistinguishable as medicaments from the inventions disclosed in documents 1-3.

Claims 18 and 19

The inventions set forth in claims 18 and 19 are not novel and do not involve an inventive step in the light of documents 4 and 5, cited in the international search report.

Given that document 4 discloses the action of Toll-like receptor TLR-2 on inflammation-inducing signals and cytokines, and document 5 discloses induction of inflammatory cytokines by human TLR (a Tol protein homologue TLR4), these can be said to suggest that production of inflammatory cytokines can be suppressed by inhibiting TLRs (document 4, page 8, lines 10-14; document 5, page 2, lines 23-28).